

Urea Substituted Imidazoquinoline Ethers

5 This application claims the benefit of previously filed Provisional Application
Serial No. 60/254,218, filed December 8, 2000.

Field of the Invention

10 This invention relates to imidazoquinoline compounds that have ether and urea
functionality at the 1-position, and to pharmaceutical compositions containing such
compounds. A further aspect of this invention relates to the use of these compounds as
immunomodulators, for inducing cytokine biosynthesis in animals, and in the treatment of
diseases, including viral and neoplastic diseases.

Background of the Invention

15 The first reliable report on the 1*H*-imidazo[4,5-*c*]quinoline ring system, Backman
et al., J. Org. Chem. 15, 1278-1284 (1950) describes the synthesis of 1-(6-methoxy-8-
quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline for possible use as an antimalarial
agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*] quinolines were
20 reported. For example, Jain et al., J. Med. Chem. 11, pp. 87-92 (1968), synthesized the
compound 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline as a possible
anticonvulsant and cardiovascular agent. Also, Baranov et al., Chem. Abs. 85, 94362
(1976), have reported several 2-oxoimidazo[4,5-*c*]quinolines, and Berenyi et al., J.
Heterocyclic Chem. 18, 1537-1540 (1981), have reported certain 2-oxoimidazo[4,5-
25 *c*]quinolines.

 Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives
thereof were later found to be useful as antiviral agents, bronchodilators and
immunomodulators. These are described in, *inter alia*, U.S. Patent Nos. 4,689,338;
4,698,348; 4,929,624; 5,037,986; 5,268,376; 5,346,905; and 5,389,640, all of which are
30 incorporated herein by reference.

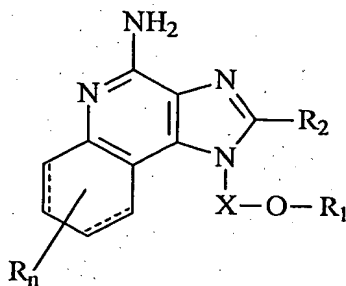
 There continues to be interest in the imidazoquinoline ring system.

Certain 1H-imidazo[4,5-c] naphthyridine-4-amines, 1H-imidazo [4,5-c] pyridin-4-amines, and 1H-imidazo[4,5-c] quinolin-4-amines having an ether containing substituent at the 1 position are known. These are described in U.S. Patent Nos. 5,268,376; 5,389,640; 5,494,916; and WO 99/29693.

Despite these attempts to identify compounds that are useful as immune response modifiers, there is a continuing need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

Summary of the Invention

We have found a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Accordingly, this invention provides imidazoquinoline-4-amine and tetrahydroimidazoquinoline-4-amine compounds that have an ether and urea containing substituent at the 1-position. The compounds are defined by Formulas (I) and (II), which are defined in more detail *infra*. These compounds share the general structural formula:



wherein X, R₁, R₂, and R are as defined herein for each class of compounds having Formulas (I) and (II).

The compounds of Formulas (I) and (II) are useful as immune response modifiers due to their ability to induce cytokine biosynthesis and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the

treatment of a variety of conditions such as viral diseases and tumors that are responsive to such changes in the immune response.

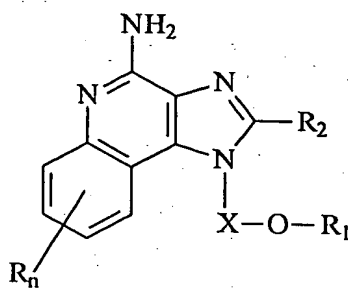
The invention further provides pharmaceutical compositions containing the immune response modifying compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral infection in an animal, and/or treating a neoplastic disease in an animal by administering a compound of Formula (I) or (II) to the animal.

In addition, the invention provides methods of synthesizing the compounds of the invention and novel intermediates useful in the synthesis of these compounds.

Detailed Description of the Invention

As mentioned earlier, we have found certain compounds that induce cytokine biosynthesis and modify the immune response in animals. Such compounds are represented by Formulas (I) and (II), as shown below.

Imidazoquinoline compounds of the invention, which have ether and urea functionality at the 1-position are represented by Formula (I):



(I)

wherein: X is -CHR₅-, -CHR₅-alkyl-, or -CHR₅-alkenyl;

R₁ is selected from the group consisting of:

-R₄-NR₈-CR₃-NR₅-Z-R₆-alkyl;

-R₄-NR₈-CR₃-NR₅-Z-R₆-alkenyl;

-R₄-NR₈-CR₃-NR₅-Z-R₆-aryl;

-R₄-NR₈-CR₃-NR₅-Z-R₆-heteroaryl;

-R₄-NR₈-CR₃-NR₅-Z-R₆-heterocyclyl;

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- R₄-NR₈-CR₃-NR₅R₇;
- R₄-NR₈-CR₃-NR₉-Z-R₆-alkyl;
- R₄-NR₈-CR₃-NR₉-Z-R₆-alkenyl;
- R₄-NR₈-CR₃-NR₉-Z-R₆-aryl;
- R₄-NR₈-CR₃-NR₉-Z-R₆-heteroaryl; and
- R₄-NR₈-CR₃-NR₉-Z-R₆-heterocyclyl;

R₂ is selected from the group consisting of:

10

- hydrogen;
- alkyl;
- alkenyl;
- aryl;
- heteroaryl;
- heterocyclyl;
- alkyl-Y-alkyl;
- alkyl-Y-alkenyl;
- alkyl-Y-aryl; and

15

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

20

- OH;
- halogen;
- N(R₅)₂;
- CO-N(R₅)₂;
- CO-C₁₋₁₀ alkyl;
- CO-O-C₁₋₁₀ alkyl;
- N₃;
- aryl;
- heteroaryl;
- heterocyclyl;
- CO-aryl; and
- CO-heteroaryl;

25

30

each **R₃** is =O or =S;

each R_4 is independently alkyl or alkenyl, which may be interrupted by one or more $-O-$ groups;

each R_5 is independently H or C_{1-10} alkyl;

R_6 is a bond, alkyl, or alkenyl, which may be interrupted by one or more $-O-$ groups;

R_7 is H or C_{1-10} alkyl which may be interrupted by a hetero atom, or R_7 can join with R_5 to form a ring;

R_8 is H, C_{1-10} alkyl, or arylalkyl; or R_4 and R_8 can join together to form a ring;

R_9 is C_{1-10} alkyl which can join with R_8 to form a ring;

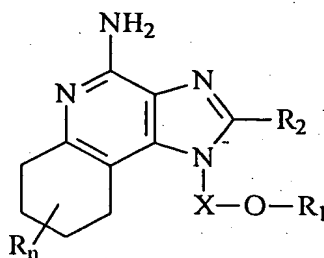
each Y is independently $-O-$ or $-S(O)_{0-2}-$;

Z is a bond, $-CO-$, or $-SO_2-$;

n is 0 to 4; and

each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen and trifluoromethyl; or a pharmaceutically acceptable salt thereof.

The invention also includes tetrahydroimidazoquinoline compounds that bear an ether and urea containing substituent at the 1-position. Such tetrahydroimidazoquinoline compounds are represented by Formula (II):



wherein: X is $-CHR_5-$, $-CHR_5$ -alkyl-, or $-CHR_5$ -alkenyl-;

R_1 is selected from the group consisting of:

$-R_4-NR_8-CR_3-NR_5-Z-R_6$ -alkyl;

$-R_4-NR_8-CR_3-NR_5-Z-R_6$ -alkenyl;

- R₄-NR₈-CR₃-NR₅-Z-R₆-aryl;
 - R₄-NR₈-CR₃-NR₅-Z-R₆-heteroaryl;
 - R₄-NR₈-CR₃-NR₅-Z-R₆-heterocyclyl;
 - R₄-NR₈-CR₃-NR₅R₇;
 - R₄-NR₈-CR₃-NR₉-Z-R₆-alkyl;
 - R₄-NR₈-CR₃-NR₉-Z-R₆-alkenyl;
 - R₄-NR₈-CR₃-NR₉-Z-R₆-aryl;
 - R₄-NR₈-CR₃-NR₉-Z-R₆-heteroaryl; and
 - R₄-NR₈-CR₃-NR₉-Z-R₆-heterocyclyl;
- R₂** is selected from the group consisting of:
- hydrogen;
 - alkyl;
 - alkenyl;
 - aryl;
 - heteroaryl;
 - heterocyclyl;
 - alkyl-Y-alkyl;
 - alkyl-Y-alkenyl;
 - alkyl-Y-aryl; and
 - alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:
- OH;
 - halogen;
 - N(R₅)₂;
 - CO-N(R₅)₂;
 - CO-C₁₋₁₀ alkyl;
 - CO-O-C₁₋₁₀ alkyl;
 - N₃;
 - aryl;
 - heteroaryl;
 - heterocyclyl;
 - CO-aryl; and

-CO-heteroaryl;

each R_3 is =O or =S;

each R_4 is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

5 each R_5 is independently H or C_{1-10} alkyl;

R_6 is a bond, alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R_7 is H or C_{1-10} alkyl which may be interrupted by a hetero atom, or R_7 can join with R_5 to form a ring;

10 R_8 is H, C_{1-10} alkyl, or arylalkyl; or R_4 and R_8 can join together to form a ring;

R_9 is C_{1-10} alkyl which can join together with R_8 to form a ring;

each Y is independently -O- or -S(O)₀₋₂;

Z is a bond, -CO-, or -SO₂-;

15 n is 0 to 4; and

each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, hydroxy, halogen, and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

Preparation of the Compounds

20 Compounds of the invention can be prepared according to Reaction Scheme I where R , R_2 , R_3 , R_4 , R_5 , R_8 , X and n are as defined above, BOC is *tert*-butoxycarbonyl and R_{11} is -Z- R_6 -alkyl, -Z- R_6 -alkenyl, -Z- R_6 -aryl, -Z- R_6 -heteroaryl, -Z- R_6 -heterocyclyl or R_{11} is R_7 where R_6 , R_7 and Z are as defined above.

25 In step (1) of Reaction Scheme I the amino group of an aminoalcohol of Formula X is protected with a *tert*-butoxycarbonyl group. A solution of the aminoalcohol in tetrahydrofuran is treated with di-*tert*-butyl dicarbonate in the presence of a base such as sodium hydroxide. Many aminoalcohols of Formula X are commercially available; others can be prepared using known synthetic methods.

30 In step (2) of Reaction Scheme I a protected aminoalcohol of Formula XI is converted to an iodide of Formula XII. Iodine is added to a solution of triphenylphosphine and imidazole in dichloromethane; then a solution of a protected aminoalcohol of Formula XI in dichloromethane is added. The reaction is carried out at ambient temperature.

In step (3) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-1-yl alcohol of Formula XIII is alkylated with an iodide of Formula XII to provide a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XIV. The alcohol of Formula XIII is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide to form an alkoxide. The iodide is added to the alkoxide solution at ambient temperature. After the addition is complete the reaction is stirred at an elevated temperature (~100°C). Many compounds of Formula XIII are known, see for example, Gerster, U.S. Patent 4,689,338; others can readily be prepared using known synthetic routes, see for example, Gerster et al., U.S. Patent No. 5,605,899 and Gerster, U.S. Patent No. 5,175,296.

In step (4) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-1-yl ether of Formula XIV is oxidized to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XV using a conventional oxidizing agent capable of forming N-oxides. Preferably a solution of a compound of Formula XIV in chloroform is oxidized using 3-chloroperoxybenzoic acid at ambient temperature.

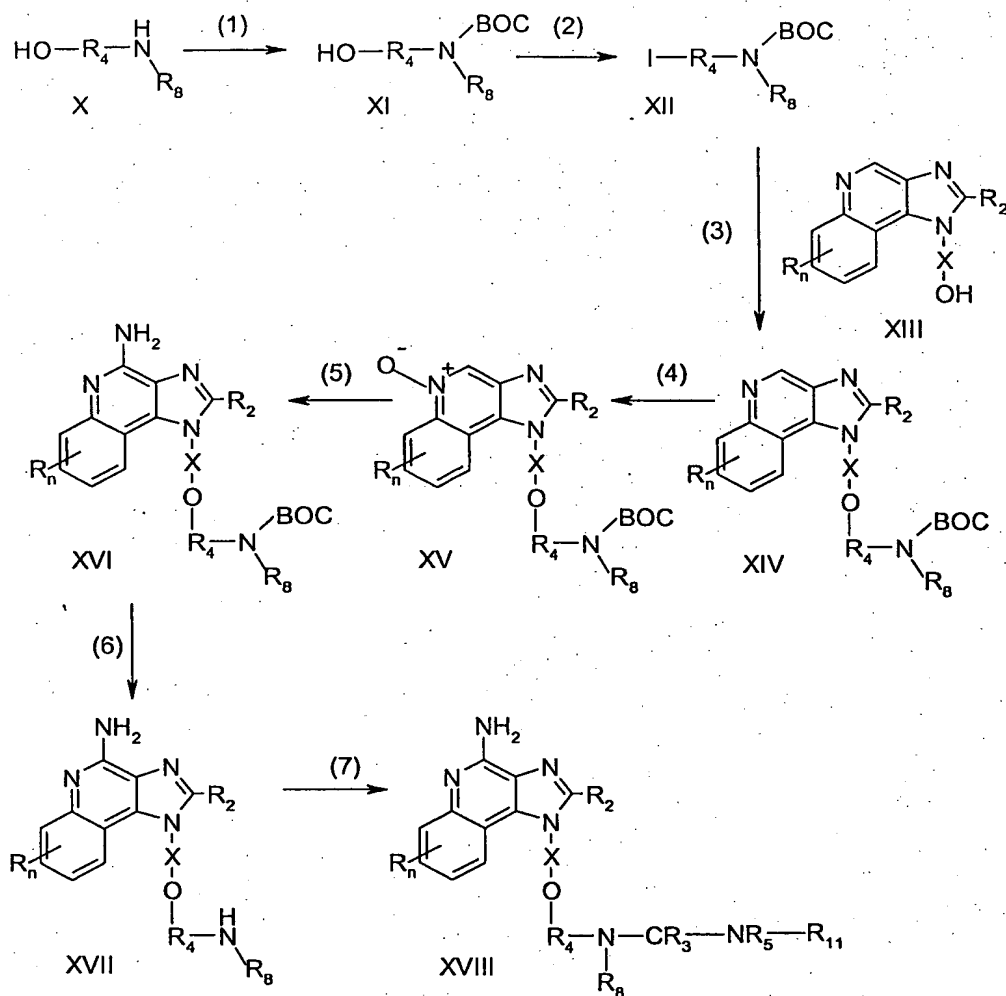
In step (5) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XV is aminated to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVI. Step (5) involves (i) reacting a compound of Formula XV with an acylating agent and then (ii) reacting the product with an aminating agent. Part (i) of step (5) involves reacting an N-oxide of Formula XV with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chlorides (e.g., benzenesulfonyl chloride, methanesulfonyl chloride, p-toluenesulfonyl chloride). Arylsulfonyl chlorides are preferred. *Para*-toluenesulfonyl chloride is most preferred. Part (ii) of step (5) involves reacting the product of part (i) with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g., in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). Ammonium hydroxide is preferred. The reaction is preferably carried out by dissolving the N-oxide of Formula XV in an inert solvent such as dichloromethane or 1,2-dichloroethane with heating if necessary, adding the aminating agent to the solution, and then slowly adding the acylating agent. Optionally the reaction can be carried out in a sealed pressure vessel at an elevated temperature (85-100°).

In step (6) of Reaction Scheme I the protecting group is removed by hydrolysis under acidic conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVII.

Preferably the compound of Formula XVI is treated with hydrochloric acid/ethanol at ambient temperature or with gentle heating.

In step (7) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVII is converted to a urea or thiourea of Formula XVIII using conventional synthetic methods. For example, a compound of Formula XVII can be reacted with an isocyanate of formula $R_{12}-N=C=O$ where R_{12} is - R_6 -alkyl, - R_6 -alkenyl, - R_6 -aryl, - R_6 -heteroaryl or - R_6 -heterocyclyl. The reaction can be carried out by adding a solution of the isocyanate in a suitable solvent such as dichloromethane or 1-methyl-2-pyrrolidinone to a solution of a compound of Formula XVII at ambient temperature. Alternatively, a compound of Formula XVII can be reacted with a thioisocyanate of formula $R_{12}-N=C=S$, an acyl isocyanate of formula $R_{12}-C(O)-N=C=O$, a sulfonyl isocyanate of formula $-R_{12}-S(O_2)-N=C=O$ or a carbamoyl chloride of formula $R_{13}-N-C(O)Cl$ where R_{13} is R_{12} or R_7 . The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R , R_2 , R_3 , R_4 , R_5 , R_8 , R_{11} , X and n are as defined above and BOC is *tert*-butoxycarbonyl.

In step (1) of Reaction Scheme II the amino group of an aminoalcohol of Formula XIX is protected with a *tert*-butoxycarbonyl group. A solution of the aminoalcohol in tetrahydrofuran is treated with di-*tert*-butyl dicarbonate in the presence of a base such as sodium hydroxide. Many aminoalcohols of Formula XIX are commercially available; others can be prepared using known synthetic methods.

In step (2) of Reaction Scheme II a protected amino alcohol of Formula XX is converted to a methanesulfonate of Formula XXI. A solution of a compound of Formula XX in a suitable solvent such as dichloromethane is treated with methanesulfonyl chloride in the presence of a base such as triethylamine. The reaction can be carried out at a
5 reduced temperature (0°C).

In step (3a) of Reaction Scheme II a methanesulfonate of Formula XXI is converted to an azide of Formula XXII. Sodium azide is added to a solution of a compound of Formula XXI in a suitable solvent such as N,N-dimethylformamide. The reaction can be carried out at an elevated temperature (80 - 100°C).

10 In step (3b) of Reaction Scheme II a compound of Formula XXII is alkylated with a halide of formula Hal-R₈ to provide a compound of Formula XXIII. In compounds where R₈ is hydrogen this step is omitted. The compound of Formula XXII is reacted with sodium hydride in a suitable solvent such as N,N-dimethylformamide or tetrahydrofuran to form the anion and then combined with the halide. The reaction can be carried out at
15 ambient temperature.

In step (4) of Reaction Scheme II an azide of Formula XXII or XXIII is reduced to provide an amine of Formula XXIV. Preferably, the reduction is carried out using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as
20 methanol or isopropanol.

In step (5) of Reaction Scheme II a 4-chloro-3-nitroquinoline of Formula XXV is reacted with an amine of Formula XXIV to provide a 3-nitroquinoline of Formula XXVI. The reaction can be carried out by adding an amine of Formula XXIV to a solution of a compound of Formula XXV in a suitable solvent such as dichloromethane in the presence
25 of a base such as triethylamine. Many quinolines of Formula XXV are known compounds or can be prepared using known synthetic methods, see for example, Gerster, U.S. Patent 4,689,338 and references cited therein.

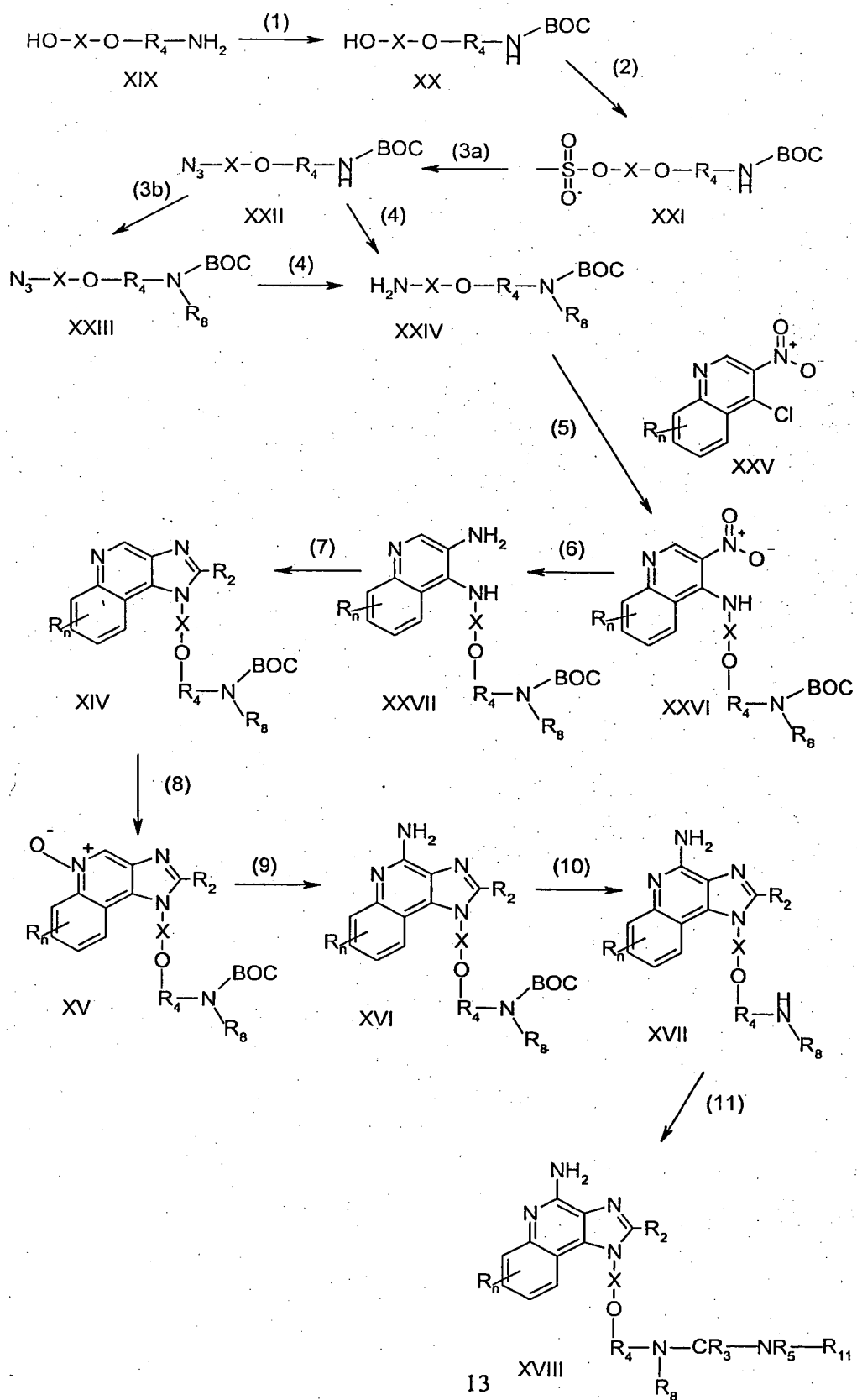
In step (6) of Reaction Scheme II a 3-nitroquinoline of Formula XXVI is reduced to provide a 3-aminoquinoline of Formula XXVII. Preferably, the reduction is carried out
30 using a conventional heterogeneous hydrogenation catalyst such as platinum on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as toluene.

In step (7) of Reaction Scheme II a compound of Formula XXVII is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XIV. Suitable equivalents to carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired R₂ substituent in a compound of Formula XIV. For example, triethyl orthoformate will provide a compound where R₂ is hydrogen and triethyl orthovalerate will provide a compound where R₂ is butyl. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalytic amount of pyridine hydrochloride can be included.

Alternatively, step (7) can be carried out by (i) reacting a compound of Formula XXVII with an acyl halide of formula R₂C(O)Cl and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula XXVII in an inert solvent such as acetonitrile or dichloromethane. The reaction can be carried out at ambient temperature or at a reduced temperature. In part (ii) the product of part (i) is heated in an alcoholic solvent in the presence of a base. Preferably the product of part (i) is refluxed in ethanol in the presence of an excess of triethylamine or heated with methanolic ammonia.

Steps (8), (9), (10) and (11) are carried out in the same manner as steps (4), (5), (6) and (7) of Reaction Scheme I.

Reaction Scheme II

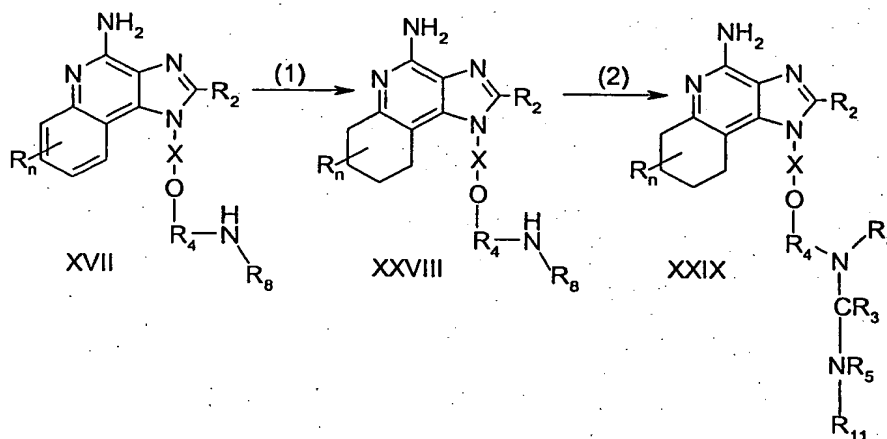


Compounds of the invention can be prepared according to Reaction Scheme III where R, R₂, R₃, R₄, R₅, R₈, R₁₁, X and n are as defined above.

In step (1) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVII is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXVIII. Preferably the reduction is carried out by suspending or dissolving a compound of Formula XVII in trifluoroacetic acid, adding a catalytic amount of platinum (IV) oxide, and then hydrogenating. The reaction can be conveniently carried out in a Parr apparatus.

Step (2) is carried out in the same manner as step (7) of Reaction Scheme I to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XXIX. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III



Compounds of the invention can also be prepared according to Reaction Scheme IV where R, R₁, R₂, X and n are as defined above.

In step (1) of Reaction Scheme IV a 4-chloro-3-nitroquinoline of Formula XXV is reacted with an amine of formula R₁-O-X-NH₂ to provide a 3-nitroquinolin-4-amine of Formula XXX. The reaction can be carried out by adding the amine to a solution of a compound of Formula XXV in a suitable solvent such as chloroform or dichloromethane

and optionally heating. Many quinolines of Formula XXV are known compounds, see for example, Gerster, U.S. Patent 4,689,338 and references cited therein.

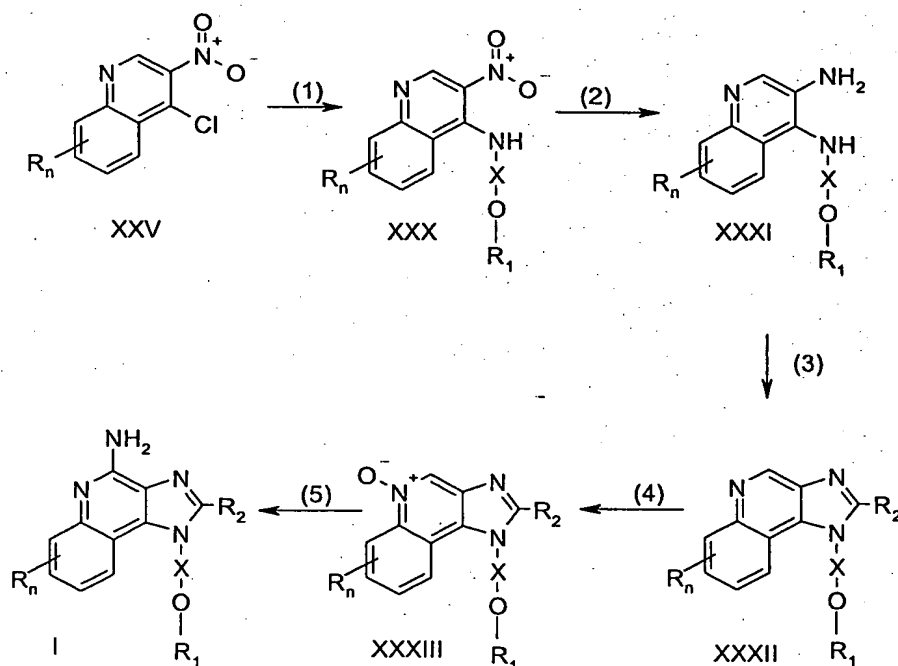
In step (2) of Reaction Scheme IV a 3-nitroquinolin-4-amine of Formula XXX is reduced using the method of step (6) of Reaction Scheme II to provide a quinoline-3,4-diamine of Formula XXXI.

In step (3) of Reaction Scheme IV a quinoline-3,4-diamine of Formula XXXI is cyclized using the method of step (7) of Reaction Scheme II to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXII.

In step (4) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXII is oxidized using the method of step (4) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXXIII.

In step (5) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinoline-5*N*-oxide of Formula XXXIII is aminated using the method of step (5) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IV



Compounds of the invention can be prepared according to Reaction Scheme V where R, R₂, R₃, R₄, R₅, R₈, R₁₁, X and n are as defined above.

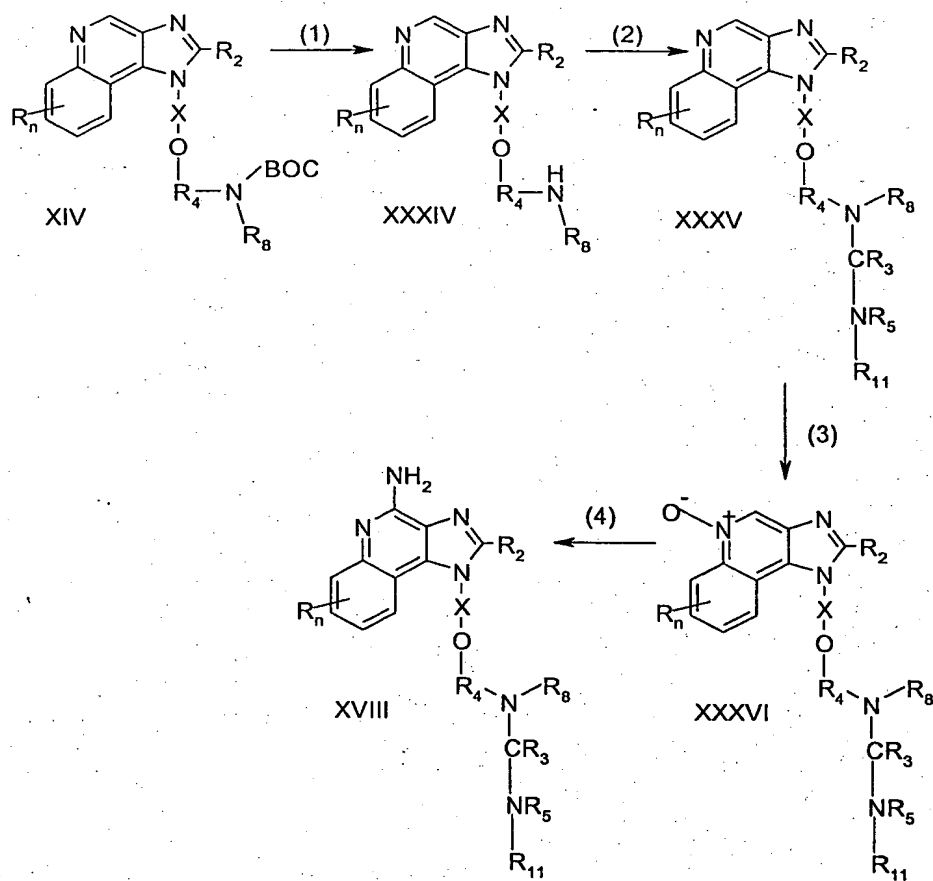
In step (1) of Reaction Scheme V the BOC group is removed from a compound of Formula XIV using the method of step (6) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIV.

In step (2) of Reaction Scheme V a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXIV is converted to a urea or thiourea of Formula XXXV using the method of step (7) of Reaction Scheme I.

In step (3) of Reaction Scheme V a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXXV is oxidized using the method of step (4) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-5*N*-oxide of Formula XXXVI.

In step (4) of Reaction Scheme V a 1*H*-imidazo[4,5-*c*]quinolin-5*N*-oxide of Formula XXXVI is aminated using the method of step (5) of Reaction Scheme I to provide a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XVIII. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V

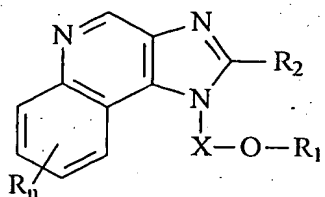


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The invention also provides novel compounds useful as intermediates in the synthesis of the compounds of Formulas (I) and (II). These intermediate compounds have the structural Formulas (III) and (IV), described in more detail below.

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One class of intermediate compounds has formula (III):



(III)

5 wherein: X is -CHR₅-, -CHR₅-alkyl-, or -CHR₅-alkenyl-;

 R₁ is selected from the group consisting of:

 -R₄-NR₈-CR₃-NR₅-Z-R₆-alkyl;

 -R₄-NR₈-CR₃-NR₅-Z-R₆-alkenyl;

 -R₄-NR₈-CR₃-NR₅-Z-R₆-aryl;

10 -R₄-NR₈-CR₃-NR₅-Z-R₆-heteroaryl;

 -R₄-NR₈-CR₃-NR₅-Z-R₆-heterocyclyl; and

 -R₄-NR₈-CR₃-NR₅R₇;

 -R₄-NR₈-CR₃-NR₉-Z-R₆-alkyl;

 -R₄-NR₈-CR₃-NR₉-Z-R₆-alkenyl;

15 -R₄-NR₈-CR₃-NR₉-Z-R₆-aryl;

 -R₄-NR₈-CR₃-NR₉-Z-R₆-heteroaryl; and

 -R₄-NR₈-CR₃-NR₉-Z-R₆-heterocyclyl;

 R₂ is selected from the group consisting of:

 -hydrogen;

20 -alkyl;

 -alkenyl;

 -aryl;

 -heteroaryl;

 -heterocyclyl;

25 -alkyl-Y-alkyl;

 -alkyl-Y-alkenyl;

 -alkyl-Y-aryl; and

- alkyl or alkenyl substituted by one or more substituents selected from the group consisting of:

-OH;
-halogen;
-N(R₅)₂;
-CO-N(R₅)₂;
-CO-C₁₋₁₀ alkyl;
-CO-O-C₁₋₁₀ alkyl;
-N₃;
-aryl;
-heteroaryl;
-heterocyclyl;
-CO-aryl; and
-CO-heteroaryl;

each R₃ is =O or =S;

each R₄ is independently alkyl or alkenyl, which may be interrupted by one or more -O- groups;

each R₅ is independently H or C₁₋₁₀ alkyl;

R₆ is a bond, or is alkyl, or alkenyl, which may be interrupted by one or more -O- groups;

R₇ is H or C₁₋₁₀ alkyl which may be interrupted by a hetero atom, or R₇ can join with R₅ to form a ring;

R₈ is H, C₁₋₁₀ alkyl, or arylalkyl; or R₄ and R₈ can join to form a ring;

R₉ is C₁₋₁₀ alkyl which can join together with R₈ to form a ring;

each Y is independently -O- or -S(O)₀₋₂;

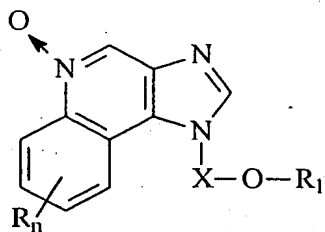
Z is a bond, -CO-, or -SO₂-;

n is 0 to 4; and

each R present is independently selected from the group consisting of C₁₋₁₀ alkyl, C₁₋₁₀ alkoxy, hydroxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

Another class of intermediate compounds are the imidazoquinoline-N-oxide compounds of Formula (IV):



(IV)

5

wherein **X** is $-\text{CHR}_5-$, $-\text{CHR}_5\text{-alkylene-}$, or $-\text{CHR}_5\text{-alkenylene-}$;

R₁ is selected from the group consisting of:

10

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{-Z-R}_6\text{-alkyl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{-Z-R}_6\text{-alkenyl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{-Z-R}_6\text{-aryl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{-Z-R}_6\text{-heteroaryl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{-Z-R}_6\text{-heterocyclyl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_5\text{R}_7$;

15

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_9\text{-Z-R}_6\text{-alkyl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_9\text{-Z-R}_6\text{-alkenyl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_9\text{-Z-R}_6\text{-aryl}$;

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_9\text{-Z-R}_6\text{-heteroaryl}$; and

$-\text{R}_4\text{-NR}_8\text{-CR}_3\text{-NR}_9\text{-Z-R}_6\text{-heterocyclyl}$;

each **Y** is independently $-\text{O}-$ or $-\text{S}(\text{O})_{0-2}-$;

20

Z is a bond, $-\text{CO}-$, or $-\text{SO}_2-$;

each **R₄** is independently alkyl or alkenyl, which may be interrupted by one or more $-\text{O}-$ groups;

each **R₅** is independently H or C_{1-10} alkyl;

25

R₆ is a bond, or is alkyl, or alkenyl, which may be interrupted by one or more $-\text{O}-$ groups;

R₇ is H or C_{1-10} alkyl which may be interrupted by a hetero atom, or **R₇** can join with **R₅** to form a ring;

R₈ is H, C_{1-10} alkyl, or arylalkyl; or **R₄** and **R₈** can join to form a ring;

R_9 is C_{1-10} alkyl which can join together with R_8 to form a ring;

n is 0 to 4; and

each R present is independently selected from the group consisting of C_{1-10} alkyl, C_{1-10} alkoxy, halogen and trifluoromethyl;

or a pharmaceutically acceptable salt thereof.

As used herein, the terms "alkyl", "alkenyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms. Preferred groups have a total of up to 10 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl and adamantyl.

In addition, the alkyl and alkenyl portions of $-X-$ groups can be unsubstituted or substituted by one or more substituents, which substituents are selected from the groups consisting of alkyl, alkenyl, aryl, heteroaryl, heterocyclyl, arylalkyl, heteroarylalkyl, and heterocyclalkyl.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl. The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxaliny, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, and so on.

"Heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring hetero atom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary

heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, and the like.

The aryl, heteroaryl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, 5 alkoxy, alkylthio, haloalkyl, haloalkoxy, haloalkylthio, halogen, nitro, hydroxy, mercapto, cyano, carboxy, formyl, aryl, aryloxy, arylthio, arylalkoxy, arylalkylthio, heteroaryl, heteroaryloxy, heteroarylthio, heteroarylalkoxy, heteroarylalkylthio, amino, alkylamino, dialkylamino, heterocyclyl, heterocycloalkyl, alkylcarbonyl, alkenylcarbonyl, alkoxy carbonyl, haloalkylcarbonyl, haloalkoxycarbonyl, alkylthiocarbonyl, arylcarbonyl, 10 heteroarylcarbonyl, aryloxy carbonyl, heteroaryloxy carbonyl, arylthiocarbonyl, heteroarylthiocarbonyl, alkanoyloxy, alkanoylthio, alkanoylamino, arylcarbonyloxy, arylcarbonylthio, alkylaminosulfonyl, alkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, aryldiazinyl, alkylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, alkylcarbonylamino, alkenylcarbonylamino, arylcarbonylamino, arylalkylcarbonylamino, 15 heteroarylcarbonylamino, heteroarylalkylcarbonylamino, alkylsulfonylamino, alkenylsulfonylamino, arylsulfonylamino, arylalkylsulfonylamino, heteroarylsulfonylamino, heteroarylalkylsulfonylamino, alkylaminocarbonylamino, alkenylaminocarbonylamino, arylaminocarbonylamino, arylalkylaminocarbonylamino, heteroarylaminocarbonylamino, heteroarylalkylaminocarbonylamino and, in the case of 20 heterocyclyl, oxo. If any other groups are identified as being "substituted" or "optionally substituted", then those groups can also be substituted by one or more of the above enumerated substituents.

Certain substituents are generally preferred. For example, preferred R_1 groups include $-R_4-NR_8-CR_3-NR_5-Z-R_6$ -alkyl and $-R_4-NR_8-CR_3-NR_5-Z-R_6$ -aryl, 25 wherein the alkyl and aryl groups can be unsubstituted or substituted; and R_4 is preferably ethylene or n-butylene or R_4 and R_8 join to form a ring. Preferably no R substituents are present (i.e., n is 0). Preferred R_2 groups include hydrogen, alkyl groups having 1 to 4 carbon atoms (i.e., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, isobutyl, and cyclopropylmethyl), methoxyethyl and ethoxymethyl. For substituted groups such as 30 substituted alkyl or substituted aryl groups, preferred substituents include halogen, nitrile, methoxy, methylthio, trifluoromethyl, and trifluoromethoxy. One or more of these

preferred substituents, if present, can be present in the compounds of the invention in any combination.

5 The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers.

Pharmaceutical Compositions and Biological Activity

10 Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound of the invention as described above in combination with a pharmaceutically acceptable carrier.

15 The term "a therapeutically effective amount" means an amount of the compound sufficient to induce a therapeutic effect, such as cytokine induction, antitumor activity, and/or antiviral activity. Although the exact amount of active compound used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg, of the compound to the subject. Any of the conventional dosage forms may be used, such as tablets, lozenges, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

25 The compounds of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, etc.

30 The compounds of the invention have been shown to induce the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds according to the invention generally include interferon- α (IFN- α) and/or tumor necrosis factor- α (TNF- α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds of the invention include IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds useful in the treatment of viral diseases and tumors. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or composition of the invention to the animal.

Certain compounds of the invention have been found to preferentially induce the expression of IFN- α in a population of hematopoietic cells such as PBMCs (peripheral blood mononuclear cells) containing pDC2 cells (precursor dendritic cell-type 2) without concomitant production of significant levels of inflammatory cytokines.

In addition to the ability to induce the production of cytokines, the compounds of the invention affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds may also activate macrophages, which in turn stimulates secretion of nitric oxide and the production of additional cytokines. Further, the compounds may cause proliferation and differentiation of B-lymphocytes.

Compounds of the invention also have an effect on the acquired immune response. For example, although there is not believed to be any direct effect on T cells or direct induction of T cell cytokines, the production of the T helper type 1 (Th1) cytokine IFN- γ is induced indirectly and the production of the T helper type 2 (Th2) cytokines IL-4, IL-5 and IL-13 are inhibited upon administration of the compounds. This activity means that the compounds are useful in the treatment of diseases where upregulation of the Th1 response and/or downregulation of the Th2 response is desired. In view of the ability of compounds of the invention to inhibit the Th2 immune response, the compounds are expected to be useful in the treatment of atopic diseases, e.g., atopic dermatitis, asthma, allergy, allergic rhinitis; systemic lupus erythematosus; as a vaccine adjuvant for cell mediated immunity; and possibly as a treatment for recurrent fungal diseases and chlamydia.

The immune response modifying effects of the compounds make them useful in the treatment of a wide variety of conditions. Because of their ability to induce the production of cytokines such as IFN- α and/or TNF- α , the compounds are particularly useful in the treatment of viral diseases and tumors. This immunomodulating activity suggests that compounds of the invention are useful in treating diseases such as, but not limited to, viral diseases including genital warts; common warts; plantar warts; Hepatitis B; Hepatitis C; Herpes Simplex Virus Type I and Type II; molluscum contagiosum; variola, particularly variola major; HIV; CMV; VZV; rhinovirus; adenovirus; influenza; and para-influenza; intraepithelial neoplasias such as cervical intraepithelial neoplasia; human papillomavirus (HPV) and associated neoplasias; fungal diseases, e.g. candida, aspergillus, and cryptococcal meningitis; neoplastic diseases, e.g., basal cell carcinoma, hairy cell leukemia, Kaposi's sarcoma, renal cell carcinoma, squamous cell carcinoma, myelogenous leukemia, multiple myeloma, melanoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, and other cancers; parasitic diseases, e.g. pneumocystis carinii, cryptosporidiosis, histoplasmosis, toxoplasmosis, trypanosome infection, and leishmaniasis; and bacterial infections, e.g., tuberculosis, and mycobacterium avium. Additional diseases or conditions that can be treated using the compounds of the invention include actinic keratosis; eczema; eosinophilia; essential thrombocythaemia; leprosy; multiple sclerosis; Ommen's syndrome; discoid lupus; Bowen's disease; Bowenoid papulosis; alopecia areata; the inhibition of Keloid formation after surgery and other types of post-surgical scars. In addition, these compounds could enhance or stimulate the healing of wounds, including chronic wounds. The compounds may be useful for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

An amount of a compound effective to induce cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes, macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN- α , TNF- α , IL-1, IL-6, IL-10 and IL-12 that is increased over the background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μ g/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising

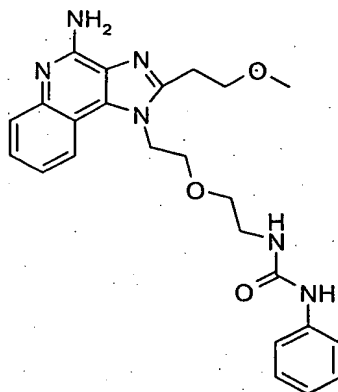
administering an effective amount of a compound or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100ng/kg to about 50mg/kg, preferably about 10µg/kg to about 5mg/kg. An amount of a compound effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 µg/kg to about 5 mg/kg.

The invention is further described by the following examples, which are provided for illustration only and are not intended to be limiting in any way.

In the examples below some of the compounds were purified using semi-preparative HPLC. A Waters Fraction Lynx automated purification system was used. The semi-prep HPLC fractions were analyzed using a Micromass LC-TOFMS and the appropriate fractions were combined and centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. The structures were confirmed by ¹H NMR.

Column: Phenomenex Luna C18(2), 10 x 50 mm, 5 micron particle size, 100Å pore; flow rate: 25 mL/min.; gradient elution from 5-65% B in 4 min., then 65 to 95 % B in 0.1 min, then hold at 95% B for 0.4 min., where A=0.05 % trifluoroacetic acid/water and B=0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering.

Age Group	Percentage of Respondents
18-29	85%
30-49	80%
50-69	75%
70+	70%



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was dried over Na₂SO₄ and concentrated to give 2-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}ethyl methanesulfonate as a brown oil (63.5 g).

Part C

A stirred solution of 2-{2-[(*tert*-butoxycarbonyl)amino]ethoxy}ethyl methanesulfonate (63.5 g, 0.224 mol) in 400 mL of N,N-dimethylformamide (DMF) was treated with NaN₃ (16.1 g, 0.247 mol) and the reaction mixture was heated to 90°C under N₂. After 5 h, the solution was cooled to room temperature and treated with 500 mL of cold H₂O. The reaction mixture was then extracted with Et₂O (3 X 300 mL). The combined organic extracts were washed with H₂O (4 X 100 mL) and brine (2 X 100 mL). The organic portion was dried over MgSO₄ and concentrated to give 52.0 g of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate as a light brown oil.

Part D

A solution of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate (47.0 g, 0.204 mol) in MeOH was treated with 4 g of 10% Pd on carbon and shaken under H₂ (3 Kg/cm²) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 35.3 g of crude *tert*-butyl 2-(2-aminoethoxy)ethylcarbamate as a colorless liquid that was used without further purification.

Part E

A stirred solution of 4-chloro-3-nitroquinoline (31.4 g, 0.151 mol) in 500 mL of anhydrous CH₂Cl₂, under N₂, was treated with triethylamine (43 mL, 0.308 mol) and *tert*-butyl 2-(2-aminoethoxy)ethylcarbamate (0.151 mol). After stirring overnight, the reaction mixture was washed with H₂O (2 X 300 mL) and brine (300 mL). The organic portion was dried over Na₂SO₄ and concentrated to give a bright yellow solid. Recrystallization from ethyl acetate/hexanes gave 43.6 g of *tert*-butyl 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethylcarbamate as bright yellow crystals.

Part F

A solution of *tert*-butyl 2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethylcarbamate (7.52 g, 20.0 mmol) in toluene was treated with 1.5 g of 5% Pt on carbon and shaken under H₂ (3 Kg/cm²) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 6.92 g of crude *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate as a yellow syrup.

Part G

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (10.2 g, 29.5 mmol) in 250 mL of anhydrous CH₂Cl₂ was cooled to 0 °C and treated with triethylamine (4.18 mL, 30.0 mmol).

5 Methoxypropionyl chloride (3.30 mL, 30.3 mmol) was then added dropwise over 5 min. The reaction was then warmed to room temperature and stirring was continued for 1 h. The reaction mixture was then concentrated under reduced pressure to give an orange solid. This was dissolved in 250 mL of EtOH and 12.5 mL of triethylamine was added. The mixture was heated to reflux and stirred under N₂ overnight. The reaction was then
10 concentrated to dryness under reduced pressure and treated with 300 mL of Et₂O. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give a brown solid. The solid was dissolved in 200 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 11.1 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as a yellow
15 syrup.

Part H

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.22 g, 24.7 mmol) in 250 mL of CHCl₃ was treated with 3-chloroperoxybenzoic acid (MCPBA, 77%, 9.12 g, 40.8 mmol). After stirring 30 min, the
20 reaction mixture was washed with 1% Na₂CO₃ solution (2 X 75 mL) and brine. The organic layer was then dried over Na₂SO₄ and concentrated to give 10.6 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as an orange foam that was used without further purification.

Part I

25 A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.6 g, 24.6 mmol) in 100 mL of 1,2-dichloroethane was heated to 60°C and treated with 10 mL of concentrated NH₄OH solution. To the rapidly stirred solution was added solid *p*-toluenesulfonyl chloride (7.05 g, 37.0 mmol) over a 10 min period. The reaction mixture was treated with an additional 1
30 mL concentrated NH₄OH solution and then sealed in a pressure vessel and heating was continued for 2 h. The reaction mixture was then cooled and treated with 100 mL of CHCl₃. The reaction mixture was then washed with H₂O, 1% Na₂CO₃ solution (2X) and

brine. The organic portion was dried over Na₂SO₄ and concentrated to give 10.6 g of *tert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate as a brown foam.

Part J

5 *Tert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethylcarbamate (10.6 g, 24.6 mmol) was treated with 75 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 1.5 h, the reaction mixture was cooled and filtered to give a gummy solid. The solid was washed EtOH and Et₂O and dried under vacuum to give the hydrochloride salt as a light brown solid. The free base
10 was made by dissolving the hydrochloride salt in 50 mL of H₂O and treating with 10% NaOH solution. The aqueous suspension was then concentrated to dryness and the residue was treated with CHCl₃. The resulting salts were removed by filtration and the filtrate was concentrated to give 3.82 g of 1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.

15 MS 330 (M + H)⁺;

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.10 (d, *J* = 8.1 Hz, 1 H); 7.66 (d, *J* = 8.2 Hz, 1 H); 7.40 (m, 1 H); 7.25 (m, 1 H); 6.88 (br s, 2 H); 4.78 (t, *J* = 5.4 Hz, 2 H); 3.89 (t, *J* = 4.8 Hz, 2 H); 3.84 (t, *J* = 6.9 Hz, 2 H); 3.54 (t, *J* = 5.4 Hz, 2 H); 3.31 (s, 3 H); 3.23 (t, *J* = 6.6 Hz, 2 H); 2.88 (t, *J* = 5.3 Hz, 2 H).

20 Part K

1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (750 mg, 2.28 mmol) was dissolved in 30 mL of anhydrous CH₂Cl₂ and cooled to 0 °C under N₂. The reaction mixture was then treated with phenyl isocyanate (247 μL, 2.28 mmol) and Et₃N (0.64 mL, 4.56 mmol) and allowed to warm slowly to room temperature.
25 After stirring for 2 h, the reaction mixture was concentrated under reduced pressure to yield a yellow solid. The yellow solid was dissolved in a minimum amount of CH₂Cl₂ and EtOAc was added until the solution became turbid. The mixture was placed in a freezer overnight and white crystal formed. The crystals were isolated by filtration and were dried under vacuum to give 126 mg of *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N'*-phenylurea. mp 171.0-174.0 °C ;
30 MS 449 (M + H)⁺;

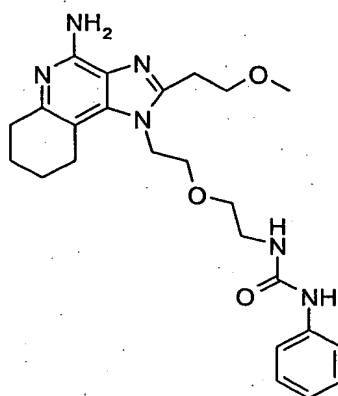
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.50 (s, 1 H); 8.05 (d, *J* = 7.7 Hz, 1 H); 7.62 (d, *J* = 8.8 Hz, 1 H); 7.44-7.18 (m, 3 H); 7.27-7.18 (m, 3 H); 6.88 (t, *J* = 7.3 Hz, 1 H); 6.54 (s, 2 H); 6.12 (t, *J* = 5.5 Hz, 2 H); 4.76 (t, *J* = 4.8 Hz, 2 H); 3.88 (t, *J* = 5.3 Hz, 2 H); 3.81 (t, *J* = 6.7 Hz, 2 H); 3.40 (t, *J* = 6.0 Hz, 2 H); 3.28 (s, 3 H); 3.25-3.14 (m, 4 H);

¹³C (75 MHz, DMSO-*d*₆) δ 155.5, 152.0, 144.9, 140.8, 132.7, 129.0, 126.8, 126.5, 121.5, 121.4, 120.5, 117.9, 115.1, 70.5, 69.4, 58.4, 45.5, 27.6;

Anal. Calcd for C₂₄H₂₈N₆O₃ • 0.21 H₂O: %C, 63.73, %H, 6.33, %N, 18.58. Found: %C, 63.33, %H, 6.28, %N, 18.67.

Example 2

N-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N'*-phenylurea



Part A

1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (10.0 g, 27.3 mmol) was dissolved in 50 mL of trifluoroacetic acid and treated with PtO₂ (1.0 g). The reaction mixture was shaken under H₂ (3 Kg/cm²). After 4 d, an additional 0.5 g of PtO₂ was added and hydrogenation was continued for an additional 3 d. The reaction was then filtered through Celite and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 200 mL of H₂O then made basic (pH~11) by addition of 10% NaOH solution. This was then extracted with CHCl₃ (5 X 75 mL) and the

combined organic layers were dried over Na₂SO₄ and concentrated to give 5.17 g of 1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan solid.

MS 334 (M + H)⁺;

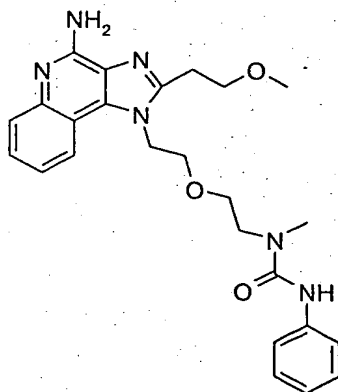
- 5 ¹H NMR (300 MHz, CDCl₃) δ 5.19 (s, 2 H); 4.49 (t, *J* = 5.4 Hz, 2 H); 3.84 (t, *J* = 6.6 Hz, 2 H); 3.71 (t, *J* = 5.4 Hz, 2 H); 3.36 (t, *J* = 5.2 Hz, 2 H); 3.51 (s, 3 H); 3.15 (t, *J* = 6.6 Hz, 2 H); 2.95 (m, 2 H); 2.82 (m, 2 H); 2.76 (t, *J* = 5.1 Hz, 2 H); 1.84 (m, 4 H), 1.47 (br s, 2 H).

Part B

- 10 1-[2-(2-Aminoethoxy)ethyl]-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (919 mg, 2.76 mmol) was dissolved in 30 mL of anhydrous CH₂Cl₂ and cooled to 0 °C under N₂. The reaction mixture was then treated with phenyl isocyanate (300 μL, 2.76 mmol) and Et₃N (0.77 mL, 5.51 mmol) and allowed to warm slowly to room temperature. After stirring overnight, the reaction mixture was
- 15 then quenched by addition of saturated NaHCO₃ solution (30 mL). The organic layer was separated and washed with H₂O and brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a yellow solid. The solid was triturated with Et₂O (30 mL) and a few drops of MeOH. The solid was isolated by filtration and dried under vacuum to give 460 mg of N-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-
- 20 *c*]quinolin-1-yl]ethoxy}ethyl)-*N'*-phenylurea as a white powder. m.p. 180-182 °C; MS 453 (M + H)⁺; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.51 (s, 1 H); 7.37 (d, *J* = 7.7 Hz, 2 H); 7.19 (t, *J* = 8.2 Hz, 2 H); 6.86 (t, *J* = 7.7 Hz, 1 H); 6.11 (t, *J* = 5.5 Hz, 2 H); 5.70 (s, 2 H); 4.43 (t, *J* = 5.1 Hz, 2 H); 3.78-3.69 (m, 4 H); 3.39 (t, *J* = 5.6 Hz, 2 H); 3.25 (s, 3 H); 3.19 (m, 2 H); 3.10 (t, *J* = 6.8 Hz, 2 H); 2.91 (m, 2 H); 2.64 (m, 2 H); 1.72 (m, 4 H);
- 25 ¹³C (75 MHz, DMSO-*d*₆) δ 155.5, 151.3, 149.3, 146.3, 140.8, 138.5, 129.0, 125.0, 121.4, 118.0, 105.6, 70.6, 70.5, 70.4, 58.4, 44.6, 39.2, 32.7, 27.6, 23.8, 23.1, 23.0; Anal. Calcd for C₂₄H₃₂N₆O₃: %C, 63.70, %H, 7.13, %N, 18.57. Found: %C, 63.33, %H, 7.16, %N, 18.66.

Example 3

N-(2-{2-[4-amino-2-(2-methoxyethyl)-
1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methyl-*N'*-phenylurea



5 Part A

Sodium hydride (60% oil dispersion, 9.1 g, 228 mmol) was placed in a round bottom flask and washed with hexanes (3X) under N₂. The dried sodium hydride was treated with 800 mL of anhydrous THF. A solution of *tert*-butyl 2-(2-azidoethoxy)ethylcarbamate (41.9 g, 182 mmol) in 200 mL of THF was then added to the stirred sodium hydride solution over 40 min. After addition was complete, the reaction was stirred an additional 20 min followed by addition of methyl iodide (13.6 mL, 218 mmol). After stirring overnight, the reaction was quenched with 300 mL of saturated NaHCO₃ solution. The reaction mixture was then treated with 200 mL of H₂O and 1 L of Et₂O. The organic phase was separated and washed with H₂O and brine. The organic portion was then dried over MgSO₄ and concentrated under reduced pressure to give 41.9 g of *tert*-butyl 2-(2-azidoethoxy)ethyl(methyl)carbamate as a yellow liquid.

Part B

A solution *tert*-butyl 2-(2-azidoethoxy)ethyl(methyl)carbamate (41.9 g, 170 mmol) in 600 mL of MeOH was treated with 2.5 g of 10% Pd on carbon and shaken under H₂ (3 Kg/cm²) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 37.2 g of crude *tert*-butyl 2-(2-aminoethoxy)ethyl(methyl)carbamate as a light yellow liquid.

Part C

A stirred solution of 4-chloro-3-nitroquinoline (32.3 g, 155 mmol) in 400 mL of anhydrous CH₂Cl₂, under N₂, was treated with triethylamine (43.1 mL, 310 mmol) and

tert-butyl 2-(2-aminoethoxy)ethyl(methyl)carbamate (37.2 g, 171 mmol). After stirring overnight, the reaction mixture was washed with H₂O (2 X 300 mL) and brine (300 mL). The organic portion was dried over Na₂SO₄ and concentrated to give a brown oil. Column chromatography (SiO₂, 33% ethyl acetate/hexanes-67% ethyl acetate/hexanes) gave 46.7 g of *tert*-butyl methyl(2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl)carbamate as a yellow solid.

Part D

A solution of *tert*-butyl methyl(2-{2-[(3-nitroquinolin-4-yl)amino]ethoxy}ethyl)carbamate (6.56 g, 16.8 mmol) in 75 mL of toluene was treated with 0.5 g of 5% Pt on carbon and shaken under H₂ (3 Kg/cm²) for 24 h. The solution was then filtered through a Celite pad and concentrated to give 6.8 g of crude *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethyl(methyl)carbamate as an orange syrup which was carried on without further purification.

Part E

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethyl(methyl)carbamate (6.05 g, 16.8 mmol) in 200 mL of anhydrous CH₂Cl₂ was cooled to 0°C and treated with triethylamine (2.40 mL, 17.2 mmol). Methoxypropionyl chloride (1.72 mL, 17.2 mmol) was then added dropwise over 5 min. The reaction was then warmed to room temperature and stirring was continued for 3 h. The reaction mixture was then concentrated under reduced pressure to give an orange solid. This was dissolved in 200 mL of EtOH and 7.2 mL of triethylamine was added. The mixture was heated to reflux and stirred under N₂ overnight. The reaction was then concentrated to dryness under reduced pressure and treated with 300 mL of Et₂O. The mixture was then filtered and the filtrate was concentrated under reduced pressure to give a brown solid. This was dissolved in 300 mL of CH₂Cl₂ and washed with H₂O and brine. The organic portion was dried over Na₂SO₄ and concentrated under reduced pressure to give a brown oil. The oil was dissolved in 100 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 7.20 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a yellow syrup.

Part F

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (7.20 g, 16.8 mmol) in 200 mL of CH₂Cl₂ was treated with MCPBA (77%, 4.32 g, 19.3 mmol). After stirring 6 h, the reaction mixture was treated with saturated NaHCO₃ solution and the layers were separated. The organic portion was washed with H₂O and brine then dried over Na₂SO₄ and concentrated to give 7.05 g of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a light brown solid.

Part G

A solution of *tert*-butyl 2-{2-[2-(2-methoxyethyl)-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (7.05 g, 15.9 mmol) in 100 mL of 1,2-dichloroethane was heated to 80°C and treated with 5 mL of concentrated NH₄OH solution. To the rapidly stirred solution was added solid *p*-toluenesulfonyl chloride (3.33 g, 17.5 mmol) over a 10 min period. The reaction mixture was treated with an additional 5 mL concentrated NH₄OH solution and then sealed in a pressure vessel and heating was continued for 4 h. The reaction mixture was then cooled and treated with 100 mL of CH₂Cl₂. The reaction mixture was then washed with H₂O, 1% Na₂CO₃ solution (3X) and brine. The organic portion was dried over Na₂SO₄ and concentrated to give 6.50 g of *tert*-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate as a brown oil.

Part H

Tert-butyl 2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl(methyl)carbamate (6.50 g, 14.7 mmol) was dissolved in 100 mL of EtOH and treated with 20 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 6 h, the reaction mixture was cooled and filtered to give a gummy solid. The solid was washed with EtOH and Et₂O and dried under vacuum to give the hydrochloride salt as a light brown powder. The free base was made by dissolving the hydrochloride salt in 50 mL of H₂O and treating with 5 mL of concentrated NH₄OH. The aqueous suspension was extracted with CH₂Cl₂ (5 X 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give 3.93 g of 2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder. MS 344 (M + H)⁺;

¹H NMR (300 MHz, DMSO-*d*₆) δ 8.07 (d, *J* = 7.7 Hz, 1 H); 7.62 (dd, *J* = 1.0, 8.3 Hz, 1 H); 7.42 (ddd, *J* = 1.0, 7.1, 8.2 Hz, 1 H); 7.22 (ddd, *J* = 1.1, 7.1, 8.2 Hz, 1 H); 6.49 (s, 2 H); 4.75 (t, *J* = 5.1 Hz, 2 H); 3.83 (t, *J* = 6.8 Hz, 4 H); 3.35 (t, *J* = 5.6 Hz, 2 H); 3.30 (s, 3 H); 3.21 (t, *J* = 6.9 Hz, 2 H); 2.45 (t, *J* = 5.6 Hz, 2 H); 2.12 (s, 3 H).

5 Part I

2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (929 mg, 2.71 mmol) was dissolved in 30 mL of anhydrous CH₂Cl₂ and treated with phenyl isocyanate (300 μL, 2.76 mmol). After stirring under N₂ overnight, the reaction mixture was concentrated under reduced pressure. Purification by
10 column chromatography (SiO₂, 3% MeOH/CHCl₃ saturated with aqueous NH₄OH) gave the product as a white solid. Crystallization from H₂O and MeOH gave 610 mg of *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methyl-*N*'-phenylurea as a flakey white crystals. m.p. 184.8-185.8 °C ;

MS 463 (M + H)⁺;

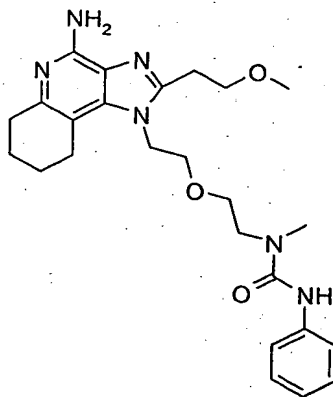
15 ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.16 (s, 1 H); 8.06 (d, *J* = 7.7 Hz, 1 H); 7.61 (dd, *J* = 1.0, 8.3 Hz, 1 H); 7.43-7.38 (m, 3 H); 7.25-7.17 (m, 3 H); 6.91 (t, *J* = 7.3 Hz, 1 H); 6.47 (s, 2 H); 4.76 (t, *J* = 5.0 Hz, 2 H); 3.88 (t, *J* = 5.1 Hz, 2 H); 3.78 (t, *J* = 6.8 Hz, 2 H); 3.48 (t, *J* = 5.2 Hz, 2 H); 3.39 (t, *J* = 5.4 Hz, 2 H); 3.27 (s, 3 H); 3.20 (t, *J* = 6.8 Hz, 2 H); 2.82 (s, 3 H);

20 ¹³C NMR (75 MHz, DMSO-*d*₆) δ 155.6, 152.0, 151.9, 145.1, 140.9, 132.7, 128.5, 126.7, 126.6, 122.0, 121.4, 120.5, 120.1, 115.1, 70.5, 69.6, 69.4, 58.4, 47.7, 45.5, 35.4, 27.6.

Anal. Calcd for C₂₅H₃₀N₆O₃•0.12 H₂O: %C, 64.62; %H, 6.56; %N, 18.08. Found: %C, 64.69; %H, 6.65; %N, 18.09.

Example 4

N-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methyl-*N*'-phenylurea



Part A

2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (4.22 g, 12.3 mmol) was dissolved in 25 mL of trifluoroacetic acid and treated with PtO₂ (0.5 g). The reaction mixture was shaken under H₂ (3 Kg/cm²). After 4 d, an additional 0.5 g of PtO₂ was added and hydrogenation was continued for an additional 3 d. The reaction was then filtered through Celite and concentrated under reduced pressure to give a yellow oil. The yellow oil was dissolved in 50 mL of H₂O and extracted with 50 mL of CHCl₃. The organic portion was removed and discarded. The aqueous portion was then made basic (pH~12) by addition of 10% NaOH solution. This was then extracted with CHCl₃ (6 X 50 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated to a brown oil. The brown oil was dissolved in 100 mL of hot MeOH and treated with 1 g of activated charcoal. The hot solution was filtered through Celite and concentrated to dryness. The resulting gummy solid was concentrated several times with Et₂O to give 3.19 g of 2-(2-methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an off-white powder.

MS 348 (M + H)⁺;

¹H NMR (300 MHz, CDCl₃) δ 4.84 (s, 2 H); 4.48 (t, *J* = 5.7 Hz, 2 H); 3.84 (t, *J* = 6.7 Hz, 2 H); 3.70 (t, *J* = 5.7 Hz, 2 H); 3.46 (t, *J* = 5.1 Hz, 2 H); 3.36 (s, 3 H); 3.14 (t, *J* = 6.7 Hz, 2 H); 2.96 (m, 2 H); 2.83 (m, 2 H); 2.65 (t, *J* = 5.1 Hz, 2 H); 2.36 (s, 3 H); 1.85 (m, 4 H).

Part B

2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (750 mg, 2.16 mmol) was dissolved in 30 mL of anhydrous CH₂Cl₂ and treated with phenyl isocyanate (239 μ L, 2.20 mmol). After stirring under N₂ overnight, the reaction mixture was concentrated under reduced pressure.

Crystallization from EtOAc and CH₂Cl₂ gave 170 mg of *N*-(2-{2-[4-amino-2-(2-methoxyethyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)-*N*-methyl-*N*'-phenylurea as fluffy white crystals. m.p. 167.7-170.0 $^{\circ}$ C ;

MS 467 (M + H)⁺;

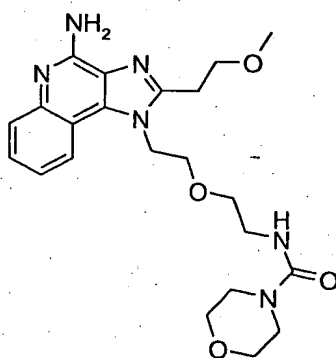
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.17 (s, 1 H); 7.43 (d, *J* = 7.6 Hz, 2 H); 7.21 (t, *J* = 7.9 Hz, 2 H); 6.91 (t, *J* = 7.3 Hz, 1 H); 5.65 (s, 2 H); 4.43 (t, *J* = 5.0 Hz, 2 H); 3.72 (t, *J* = 7.0 Hz, 2 H); 3.70 (t, *J* = 5.2 Hz, 2 H); 3.46-3.41 (m, 4 H); 3.24 (s, 3 H); 3.07 (t, *J* = 6.9 Hz, 2 H); 2.92 (m, 2 H); 2.85 (s, 3 H); 2.64 (m, 2 H); 1.72 (m, 4 H);

¹³C NMR (75 MHz, DMSO-*d*₆) δ 155.6, 151.2, 149.3, 146.3, 140.9, 138.4, 128.5, 124.9, 122.0, 120.1, 105.5, 70.7, 70.5, 69.5, 58.4, 48.0, 44.6, 35.5, 32.8, 27.6, 23.8, 23.1, 23.0.

Anal. Calcd for C₂₅H₃₄N₆O₃: %C, 64.36; %H, 7.35; %N, 18.01. Found: %C, 64.04; %H, 7.38; %N, 18.02.

Example 5

N-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)morpholine-4-carboxamide



Under a nitrogen atmosphere, 1-[2-(2-aminoethoxy)ethyl]-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (0.75 g, 2.3 mmol) was dissolved in dichloromethane (30

mL) and triethylamine (0.64 mL, 4.6 mmol) using mild heat and vigorous stirring. The solution was chilled in an ice-water bath and 4-morpholinecarbonyl chloride (0.27 mL, 2.3 mmol) was added dropwise. The cooling bath was removed and the reaction was stirred for an additional 4 hours. The reaction was quenched by the addition of saturated sodium bicarbonate solution (25 mL). The phases were separated and the organic layer was washed with water (3 × 25 mL), brine (25 mL), dried (Na₂SO₄), filtered and concentrated to yield a yellow foam. The product was recrystallized from dichloromethane and ethyl acetate. The crystals were triturated with ether (2 × 5 mL) to remove residual solvent. The final product was dried in a vacuum oven to provide 200 mg of N-(2-{2-[4-amino-2-(2-methoxyethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]ethoxy}ethyl)morpholine-4-carboxamide as a tan crystalline solid, m.p. 164-166 °C.

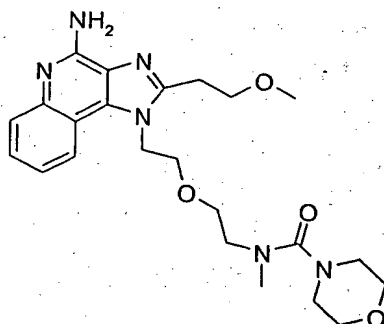
¹H NMR (300 MHz, DMSO-*d*₆) δ 8.06 (d, *J* = 8.1 Hz, 1 H), 7.61 (d, *J* = 7.3 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 1 H), 7.23 (t, *J* = 7.8 Hz, 1 H), 6.51 (s, 2 H), 6.33 (t, *J* = 5.0 Hz, 1 H), 4.74 (t, *J* = 4.3 Hz, 2 H), 3.85-3.81 (m, 4 H), 3.49 (t, *J* = 4.3 Hz, 4 H), 3.33 (t, *J* = 5.9 Hz, 2 H), 3.30 (s, 3 H), 3.21 (t, *J* = 6.8 Hz, 2 H), 3.14 (t, *J* = 4.5 Hz, 4 H), 3.08 (t, *J* = 6.0 Hz, 2 H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 157.8, 151.9, 145.0, 132.7, 126.7, 126.6, 121.4, 120.5, 115.1, 70.4, 70.2, 69.2, 58.4, 45.5, 44.0, 27.6;

Anal. Calcd for C₂₂H₃₀N₆O₄: %C, 59.71, %H, 6.83, %N, 18.99. Found: %C, 59.71, %H, 6.80, %N, 18.78;

MS(CI) *m/e* 443 (M+H)

Example 6

N-(2-{2-[4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-N-methylmorpholine-4-carboxamide.



2-(2-Methoxyethyl)-1-{2-[2-(methylamino)ethoxy]ethyl}-1H-imidazo[4,5-c]quinolin-4-amine (802 mg, 2.34 mmol) was dissolved in 30 mL of anhydrous CH_2Cl_2 and cooled to 0°C under N_2 . To the stirred solution were added Et_3N (0.65 mL, 4.68 mmol) and morpholinecarbonyl chloride (273 μL , 2.34 mmol) and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then quenched by addition of saturated NaHCO_3 solution (30 mL) and CH_2Cl_2 (30 mL). The organic layer was separated and washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (SiO_2 , 2-5% $\text{MeOH}/\text{CHCl}_3$ saturated with aqueous NH_4OH) gave the product as a colorless foam. Crystallization from EtOAc gave 640 mg of N-(2-{2-[4-amino-2-(2-methoxyethyl)-1H-imidazo[4,5-c]quinolin-1-yl]ethoxy}ethyl)-N-methylmorpholine-4-carboxamide as white crystals. $\text{Mp} = 121.8\text{-}122.3^\circ\text{C}$.

MS 457 ($\text{M} + \text{H}$) $^+$;

^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.06 (dd, $J = 0.9, 8.3$ Hz, 1 H); 7.61 (dd, $J = 1.1, 8.3$ Hz, 1 H); 7.41 (ddd, $J = 1.2, 7.0, 8.3$ Hz, 1 H); 7.22 (ddd, $J = 1.3, 7.0, 8.1$ Hz, 1 H); 6.44 (s, 2 H); 4.74 (t, $J = 5.2$ Hz, 2 H); 3.84 (t, $J = 5.2$ Hz, 2 H); 3.82 (t, $J = 6.9$ Hz, 2 H); 3.50-3.43 (m, 6 H); 3.30 (s, 3 H); 3.20 (t, $J = 6.9$ Hz, 2 H); 3.16 (t, $J = 5.5$ Hz, 2 H); 2.88 (t, $J = 4.7$ Hz, 4 H); 2.59 (s, 3 H);

^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 163.8, 152.0, 151.8, 145.2, 132.7, 126.7, 121.3, 120.6, 115.1, 70.4, 69.4, 68.9, 66.1, 58.5, 49.1, 47.3, 45.5, 36.9, 27.7.

Anal. Calcd for $\text{C}_{23}\text{H}_{32}\text{N}_6\text{O}_4$: %C, 60.51; %H, 7.07; %N, 18.41. Found: %C, 60.56; %H, 6.85; %N, 18.19.

Examples 7 -21

5 Part A

A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (3.46 g, 10.0 mmol) in 50 mL of toluene was treated with triethylorthovalerate (2.5 mL, 14.5 mmol) and the reaction mixture was heated to reflux. A 25 mg portion of pyridinium hydrochloride was then added and refluxing was continued for 4 h. The reaction was then concentrated to dryness under reduced pressure. The residue was dissolved in 50 mL of CH₂Cl₂ and washed with saturated NaHCO₃, H₂O and brine. The organic portion was dried over Na₂SO₄ and concentrated to give a green oil. The green oil was dissolved in 50 mL of hot MeOH and treated with activated charcoal. The hot solution was filtered and concentrated to give 4.12 g of *tert*-butyl 2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a yellow oil.

15 Part B

A solution of *tert*-butyl 2-[2-(2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (4.12 g, 10.0 mmol) in 50 mL of CH₂Cl₂ was treated with 3-chloroperoxybenzoic acid (MCPBA, 77%, 2.5 g, 11.2 mmol). After stirring for 5 h, the reaction mixture was treated with saturated NaHCO₃ solution and the layers were separated. The organic portion was washed with H₂O and brine then dried over Na₂SO₄ and concentrated to give 3.68 g of *tert*-butyl 2-[2-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

20 Part C

A solution of *tert*-butyl 2-[2-(2-butyl-5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (3.68 g, 8.60 mmol) in 100 mL of 1,2-dichloroethane was heated to 80 °C and treated with 10 mL of concentrated NH₄OH solution. To the rapidly stirred solution was added solid *p*-toluenesulfonyl chloride (1.87 g, 9.81 mmol) over a 10 min period. The reaction mixture was then sealed in a pressure vessel and heating was continued for 2 h. The reaction mixture was then cooled and treated with 100 mL of CH₂Cl₂. The reaction mixture was then washed with H₂O, 1% Na₂CO₃ solution (3X) and brine. The organic portion was dried over Na₂SO₄ and concentrated to give 3.68 g of *tert*-

butyl 2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part D

Tert-butyl 2-[2-(4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (3.68 g, 8.60 mmol) was suspended in 20 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 3 h, the reaction mixture was concentrated to give a solid. The solid was triturated with hot EtOH (50 mL) and filtered to give 2.90 g of the product as the hydrochloride salt. The free base was made by dissolving the hydrochloride salt in 50 mL of H₂O and treating with 5 mL of concentrated NH₄OH. The aqueous suspension was extracted with CH₂Cl₂ (3 X 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give 1-[2-(2-aminoethoxy)ethyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.

MS 328 (M + H)⁺;

¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, *J* = 8.3 Hz, 1 H); 7.83 (d, *J* = 8.4 Hz, 1 H); 7.50 (m, 1 H); 7.30 (m, 1 H); 5.41 (s, 2 H); 4.69 (t, *J* = 5.6 Hz, 2 H); 3.93 (t, *J* = 5.6 Hz, 2 H); 3.39 (t, *J* = 5.1 Hz, 2 H); 2.97 (t, *J* = 7.9 Hz, 2 H); 2.76 (t, *J* = 5.1 Hz, 2 H); 1.89 (m, 2 H); 1.52 (m, 2 H); 1.26 (br s, 2 H); 1.01 (t, *J* = 7.3 Hz, 3 H).

Part E

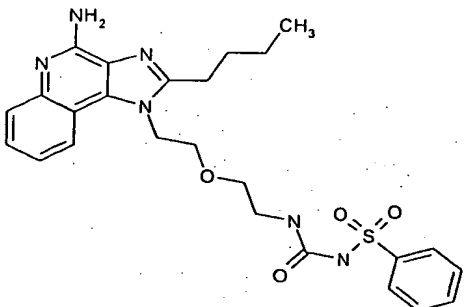
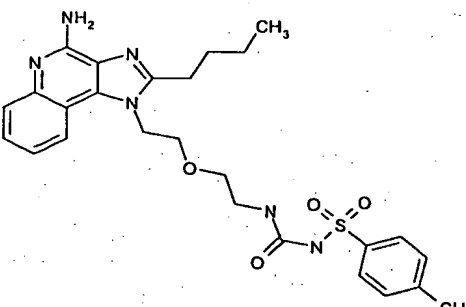
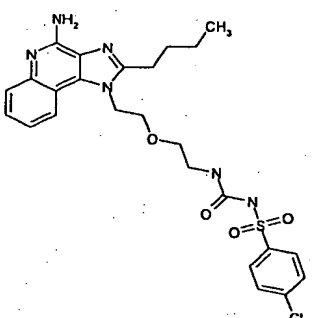
The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme I above using the following general method.

The isocyanate (84 μmol.) was added to a test tube containing a solution of 1-[2-(2-aminoethoxy)ethyl]-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-4-amine (25 mg, 76 μmol) in dichloromethane (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum centrifugation. The residue was purified by semi-preparative HPLC using the method described above. The table below shows the structure of the free base and the observed accurate mass (M + H).

Example Number	Structure of Free Base	Accurate Mass (obs.)
7		413.2644
8		427.2841
9		427.2823
10		447.2496

Example Number	Structure of Free Base	Accurate Mass (obs.)
11		441.2638
12		453.2980
13		472.2457
14		477.2611

Example Number	Structure of Free Base	Accurate Mass (obs.)
15		487.2804
16		490.2919
17		493.2386
18		207.2741

Example Number	Structure of Free Base	Accurate Mass (obs.)
19		511.2120
20		525.2280
21		545.1758

Examples 22 - 36

5 Part A

Using the general method of Part A of Examples 7 - 21, 4-piperidine ethanol (10 g, 77.4 mmol) was reacted with di-*tert*-butyl dicarbonate (17.7 g, 81.3 mmol) to provide 13.1 g of *tert*-butyl 4-(2-hydroxyethyl)piperidine-1-carboxylate as a clear oil.

Part B

10 Iodine (7.97 g) was added in three portions to a solution of imidazole (3.89 g, 57.1 mmol) and triphenylphosphine (14.98 g, 57.1 mmol) in dichloromethane (350 mL). After

5 minutes a solution of the material from Part A in dichloromethane (70 mL) was added. The reaction mixture was stirred at ambient temperature overnight. More iodine (7.97 g) was added and the reaction was stirred at ambient temperature for 1 hr. The reaction mixture was washed with saturated sodium thiosulfate (2X) and brine, dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide an oily residue. The residue was purified by column chromatography (silica gel eluting with 20% ethyl acetate in hexanes) to provide 15.52 g of *tert*-butyl 4-(2-iodoethyl)piperidine-1-carboxylate as a pale yellow oil.

Part C

Under a nitrogen atmosphere, 2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butan-1-ol (6.5 g, 26.9 mmol) was added in three portions to a suspension of sodium hydride (1.4 g of 60%, 35.0 mmol) in anhydrous *N,N*-dimethylformamide. The reaction mixture was allowed to stir for 45 minutes by which time gas evolution had ceased. *Tert*-butyl 4-(2-iodoethyl)piperidine-1-carboxylate (10.05 g, 29.6 mmol) was added dropwise over a period of 15 minutes. The reaction mixture was allowed to stir at ambient temperature for 2.5 hrs; then it was heated to 100°C and stirred overnight. Analysis by HPLC showed that the reaction was about 35% complete. Saturated ammonium chloride solution was added, the resulting mixture was allowed to stir for 20 minutes and then it was extracted with ethyl acetate (2X). The ethyl acetate extracts were washed with water (2X) and then with brine, combined, dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide a brown oil. The oil was purified by column chromatography (silica gel eluting sequentially with 30% ethyl acetate in hexanes, 50% ethyl acetate in hexanes, and ethyl acetate) to provide 2.2 g of *tert*-butyl 4-{2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate.

Part D

Using the general method of Examples 7 - 21 Part H, the material from Part C was oxidized to provide *tert*-butyl 4-{2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate as an oil.

Part E

Ammonium hydroxide solution (20 mL) was added to a solution of the material from Part D in dichloromethane (20 mL). A solution of tosyl chloride (0.99 g, 5.2 mmol) in dichloromethane (10 mL) was added over a period of 5 minutes. The resulting biphasic

reaction mixture was allowed to stir overnight. The reaction mixture was diluted with chloroform and saturated sodium bicarbonate solution. The layers were separated. The organic layer was dried over sodium sulfate, filtered and then concentrated under reduced pressure to provide a brown glass. This material was purified by column chromatography (silica gel eluting first with 50% ethyl acetate in hexanes and then with ethyl acetate) to provide 1.0 g of *tert*-butyl 4-{2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate as pale yellow glassy foam.

Part F

Under a nitrogen atmosphere, *tert*-butyl 4-{2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)butoxy]ethyl}piperidine-1-carboxylate (1.00 g, 2.1 mmol) and 2*N* ethanolic hydrochloric acid (10 ml, 20 mmol) were combined and the solution was stirred at ambient temperature for 14 hours. The solvent was removed *in vacuo* and the resulting tan solid was dissolved in water. Saturated aqueous sodium carbonate was added until the pH reached 10. After extraction with dichloromethane (3X), the organic fractions were combined, washed with brine, dried (Na₂SO₄), filtered, and the majority of the solvent was removed *in vacuo*. Hexane was added to form a precipitate. Vacuum filtration yielded 0.5 g of 1-{1-[(2-piperidin-4-ylethoxy)methyl]propyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.

¹H-NMR (300MHz, DMSO-*d*₆): δ 8.34 (bs, 1H), 8.19 (d, *J* = 8.49Hz, 1H), 7.61 (dd, *J* = 8.31, 1.13Hz, 1H), 7.45-7.39 (m, 1H), 7.25-7.19 (m, 1H), 6.55 (s, 2H), 5.25-5.15 (m, 1H), 4.00-3.80 (m, 2H), 3.5-3.3 (m, 2H), 2.8-2.64 (m, 2H), 2.22-2.11 (m, 2H), 2.09-1.99 (m, 2H), 1.8-1.63 (bs, 1H), 1.37-1.0 (m, 5H), 0.95-0.7 (m, 5H);

¹³C-NMR (75MHz, DMSO-*d*₆): δ 152.8, 145.8, 140.6, 133.0, 127.8, 127.0, 126.9, 121.3, 121.0, 115.5, 71.8, 68.1, 58.4, 46.1, 36.3, 33.1, 32.7, 24.5, 9.9;

MS (CI) *m/e* 368.2459 (368.2450 calcd for C₂₁H₃₀N₅O).

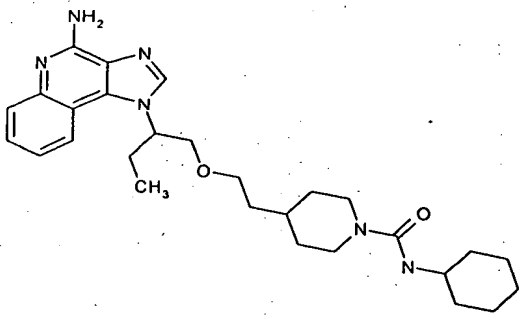
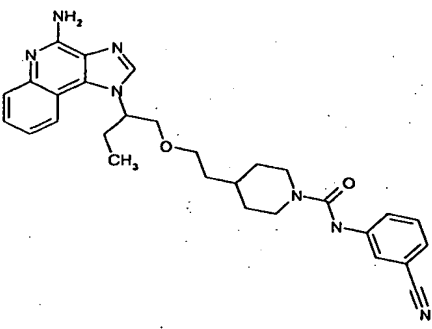
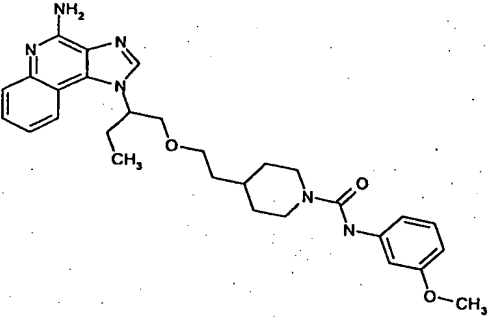
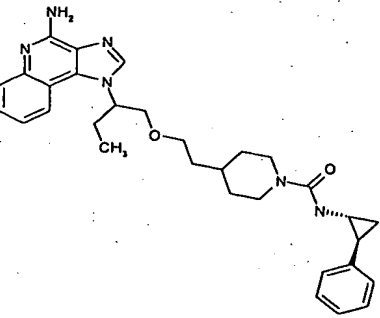
Part G

The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme I above using the following general method.

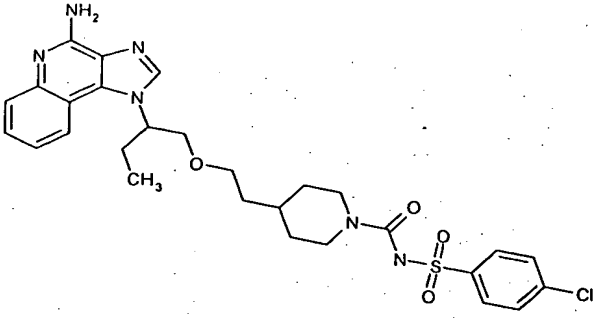
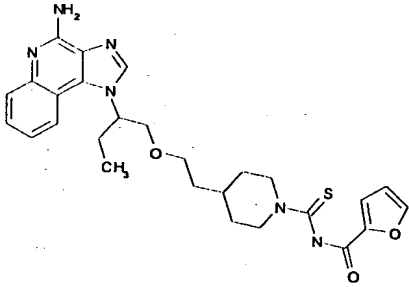
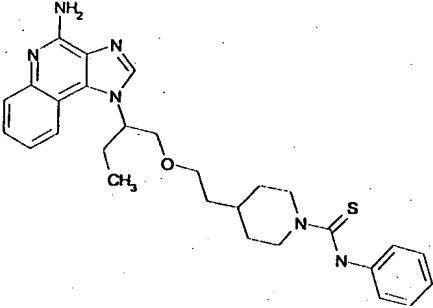
The isocyanate or isothiocyanate (75 μmol.) was added to a test tube containing a solution of 1-{1-[(2-piperidin-4-ylethoxy)methyl]propyl}-1*H*-imidazo[4,5-*c*]quinolin-4-amine (25 mg, 68 μmol) in dichloromethane (5 mL). The test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum

centrifugation. The residue was purified by semi-preparative HPLC using the method described above. The table below shows the structure of the free base and the observed accurate mass ($M + H$).

Example Number	Structure of Free Base	Accurate Mass (obs.)
22		453.2983
23		467.3138
24		487.2787
25		481.2930

Example Number	Structure of Free Base	Accurate Mass (obs.)
26		493.3270
27		512.2757
28		517.2907
29		527.3112

Example Number	Structure of Free Base	Accurate Mass (obs.)
30		529.2911
31		533.2704
32		547.3032
33		565.2641

Example Number	Structure of Free Base	Accurate Mass (obs.)
34		585.2056
35		521.2297
36		503.2589

5

Examples 37 - 44

Part A

10 A solution of *tert*-butyl 2-{2-[(3-aminoquinolin-4-yl)amino]ethoxy}ethylcarbamate (6.92 g, 20.0 mmol) in 100 mL of toluene was treated with triethylorthoformate (4.65 mL, 28.0 mmol) and the reaction mixture was heated to reflux. A 100 mg portion of pyridinium hydrochloride was then added and refluxing was continued for 2 h. The reaction was then concentrated to dryness under reduced pressure.

The residue was dissolved in 200 mL of CH_2Cl_2 and washed with saturated NaHCO_3 , H_2O and brine. The organic portion was dried over Na_2SO_4 and concentrated to give a green oil. The green oil was dissolved in 200 mL of hot MeOH and treated with 10 g of activated charcoal. The hot solution was filtered and concentrated to give 5.25 g of *tert*-butyl 2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light yellow syrup.

Part B

A solution of *tert*-butyl 2-[2-(1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (5.25 g, 14.7 mmol) in 200 mL of CH_2Cl_2 was treated with MCPBA (77%, 3.63 g, 16.3 mmol). After stirring overnight, the reaction mixture was treated with saturated NaHCO_3 solution and the layers were separated. The organic portion was washed with H_2O and brine then dried over Na_2SO_4 and concentrated to give 4.60 g of *tert*-butyl 2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part C

A solution of *tert*-butyl 2-[2-(5-oxido-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (4.60 g, 12.4 mmol) in 150 mL of 1,2-dichloroethane was heated to 80 °C and treated with 10 mL of concentrated NH_4OH solution. To the rapidly stirred solution was added solid *p*-toluenesulfonyl chloride (2.71 g, 14.2 mmol) over a 10 min period. The reaction mixture was treated with an additional 2 mL of concentrated NH_4OH solution and then sealed in a pressure vessel and heating was continued for 3 h. The reaction mixture was then cooled and treated with 100 mL of CH_2Cl_2 . The reaction mixture was then washed with H_2O , 1% Na_2CO_3 solution (3X) and brine. The organic portion was dried over Na_2SO_4 and concentrated to give 4.56 g of *tert*-butyl 2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate as a light brown foam.

Part D

Tert-butyl 2-[2-(4-amino-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethoxy]ethylcarbamate (4.56 g, 12.3 mmol) was dissolved in 100 mL of EtOH and treated with 30 mL of 2M HCl in EtOH and the mixture was heated to reflux with stirring. After 3 h, the reaction mixture was concentrated to give a solid. The solid was triturated with hot EtOH (100 mL) and filtered to give the product as the hydrochloride salt. The free base was made by dissolving the hydrochloride salt in 50 mL of H_2O and treating with 5 mL of concentrated

NH₄OH. The aqueous suspension was extracted with CH₂Cl₂ (5 X 50 mL). The combined organic layers were dried over Na₂SO₄ and concentrated to give 1.35 g of 1-[2-(2-aminoethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a tan powder.

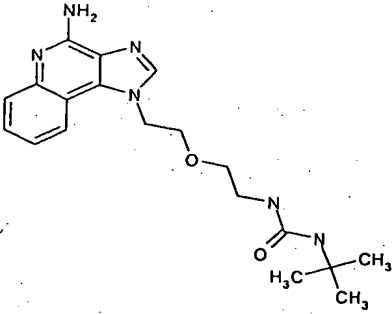
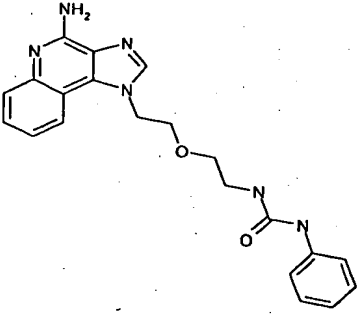
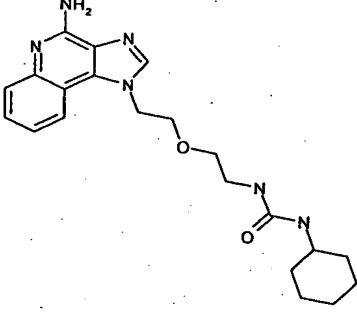
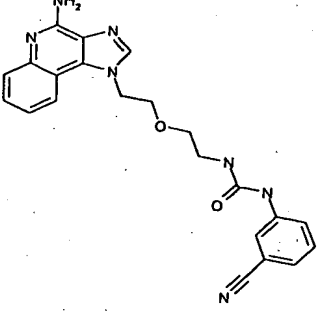
MS 272 (M + H)⁺;

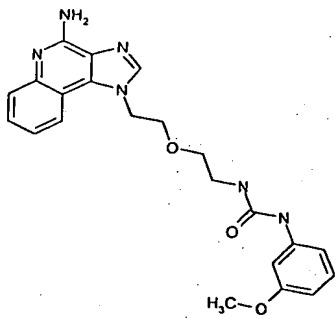
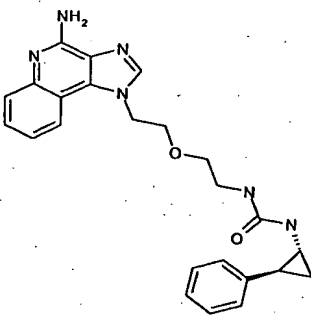
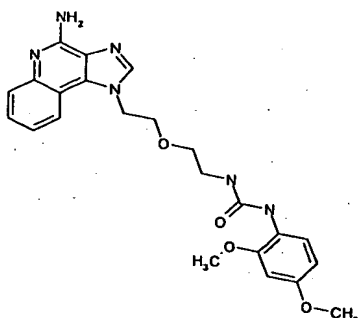
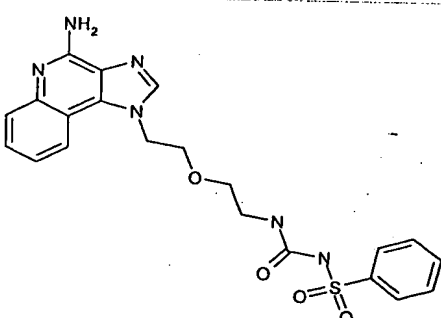
5 ¹H NMR (300 MHz, CDCl₃) δ 7.98 (d, *J* = 8.2 Hz, 1 H); 7.88 (s, 1 H); 7.84 (d, *J* = 8.4 Hz, 1 H); 7.54 (m, 1 H); 7.32 (m, 1 H); 5.43 (s, 2 H); 4.74 (t, *J* = 5.2 Hz, 2 H); 3.97 (t, *J* = 5.2 Hz, 2 H); 3.42 (t, *J* = 5.1 Hz, 2 H); 2.78 (t, *J* = 5.1 Hz, 2 H); 1.10 (br s, 2 H).

Part E

10 The compounds in the table below were prepared according to the synthetic method of step (7) of Reaction Scheme I above using the following general method.

15 1-[2-(2-Aminoethoxy)ethyl]-1*H*-imidazo[4,5-*c*]quinolin-4-amine (20 mg, 74 μmol) and 1-methyl-2-pyrrolidinone (5 mL) were combined in a test tube and then sonicated with heating to provide a solution. The isocyanate (81 μmol.) was added, the test tube was capped and then placed on a shaker at ambient temperature for 20 hr. The solvent was removed by vacuum centrifugation. The residue was purified by semi-preparative HPLC using the method described above. The table below shows the structure of the free base and the observed accurate mass (M + H).

Example Number	Structure of Free Base	Accurate Mass (obs.)
37		371.2204
38		391.1884
39		397.2373
40		416.1844

Example Number	Structure of Free Base	Accurate Mass (obs.)
41		421.1946
42		431.2206
43		451.2115
44		455.1513

CYTOKINE INDUCTION IN HUMAN CELLS

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN and TNF, respectively) secreted into culture media as described by Testerman et. al. in
5 "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", Journal of Leukocyte Biology, 58, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMCs) are separated from whole
10 blood by density gradient centrifugation using Histopaque®-1077. The PBMCs are washed twice with Hank's Balanced Salts Solution and then are suspended at $3-4 \times 10^6$ cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

15 The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells.

Incubation

20 The solution of test compound is added to the first well containing RPMI complete and serial dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range. The final concentration of PBMC suspension is $1.5-2 \times 10^6$ cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at
25 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 5-10 minutes at 1000 rpm (~200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile
polypropylene pipet and transferred to sterile polypropylene tubes. Samples are
30 maintained at -30 to -70°C until analysis. The samples are analyzed for interferon (α) and for tumor necrosis factor (α) by ELISA.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

- 5 Tumor necrosis factor (α) concentration is determined using ELISA kits available from Genzyme, Cambridge, MA; R&D Systems, Minneapolis, MN; or Pharmingen, San Diego, CA. Results are expressed in pg/mL.

10 The table below lists the lowest concentration found to induce interferon and the lowest concentration found to induce tumor necrosis factor for each compound. A “*” indicates that no induction was seen at any of the tested concentrations; generally the highest concentration tested was 10 or 30 μ M.

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μ M)	
	Interferon	Tumor Necrosis Factor
3	0.01	0.37
7	0.0001	10
8	0.0001	10
9	0.0001	1
10	0.0001	10
11	0.0001	0.1
12	0.0001	1
13	0.0001	1
14	0.0001	10
15	0.0001	0.1
16	0.0001	10
17	*	10
18	1	*
19	0.1	10
20	0.01	10

Cytokine Induction in Human Cells		
Example Number	Lowest Effective Concentration (μ M)	
	Interferon	Tumor Necrosis Factor
21	1	10
22	0.1	1
23	1	1
24	0.1	1
25	0.1	1
26	0.1	1
27	0.1	1
28	0.1	1
29	0.1	1
30	1	1
31	1	10
32	0.1	1
33	1	10
34	1	10
35	1	1
36	0.1	*
37	10	10
38	10	10
39	10	10
40	10	10
41	10	10
42	10	*
43	10	10
44	*	*